# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>050036woMest | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/EP2005/050812 | International filing date *(day/month/year)*<br>25.02.2005 | Priority date *(day/month/year)*<br>27.02.2004 |
| International Patent Classification (IPC) or national classification and IPC<br>INV. C07K16/06 A61L2/00 | | |
| Applicant<br>OCTAPHARMA AG et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☒ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 04.01.2006 | 14.06.2006 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Niebuhr-Ebel, K<br>Telephone No. +49 89 2399-7814 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/050812

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-14 as originally filed

**Claims, Numbers**

1-23 received on 04.01.2006 with letter of 21.12.2005

**Drawings, Sheets**

1/2, 2/2 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/050812

## Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 2-4, 6, 8-23 |
| | No: | Claims | 1, 5, 7 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-23 |
| Industrial applicability (IA) | Yes: | Claims | 1-23 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

## Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

## Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

V.1. The present invention discloses a method of preparing a purified, virus inactivated antibody preparation by adding caprylate to the starting solution and subsequently passing the filtered supernatant over an anion exchange chromatography.

V.2. Reference is made to the following documents:

D1: M. STEINBUCH ET R. AUDRAN: "Isolement de l'immunoglobuline IgG du plasma humain à l'aide de l'acide caprylique" REV. FRANC. ETUDES CLIN. ET BIOL., vol. 14, 1969, pages 1054-1058, XP001197292

D2: HABEEB A F S A AND FRANCIS R D: "Preparation of human immunoglobuilin by caprylic acid precipitation" PREPARATIVE BIOCHEMISTRY, NEW YORK, NY, US, vol. 14, no. 1, 1984, pages 1-17, XP002078264

D3: EP-A-0 893 450 (BAYER CORPORATION) 27 January 1999 (1999-01-27)

D4: LUNDBLAD J L ET AL: "INACTIVATION OF LIPID-ENVELOPED VIRUSES IN PROTEINS BY CAPRYLATE" VOX SANGUINIS, S. KARGER AG, BASEL, CH, vol. 60, no. 2, 1991, pages 75-81, XP008033429 ISSN: 0042-9007

**Novelty (Art. 33 (2) PCT)**

V.3. D1, cited by the applicant, and D2 both disclose a method of preparing human immunoglobulin starting from human plasma. In D1, the plasma preparations were dissolved in citrate buffer and actetate buffer added, so that "the pH generally lowers to 4.8" (p. 1054, right column, lines 10/11), before the caprylic acid is added. At the end of this paragraph, it is stated that the IgG yield can be increased by washing the precipitate with an acetate buffer, pH 4.8. On page 1055, right column, l. 3-4, a statement is made that the pH the authors finally chose for the plasma/buffer mixture was 4.8.
In D2 the plasma was diluted with "acetate buffer pH 4, and the final pH was adjusted to 4.8 with 1N acetic acid", before caprylic acid was added (p. 2, l. 11-15).

After centrifugation and filtration the supernatant is adjusted to pH 5.7 and passed over a DEAE-cellulose column, i.e. an anion-exchange resin.
Due to the intrinsic property of caprylate, which is known to rapidly and effectively inactivate virus particles over a wide range of conditions (D4), the solution is considered virus-inactivated. Therefore the term "virus safe antibody preparation" does not render the method per se novel.

V.4. D1 and D2 are considered to fall under the scope of claims 1, 5 and 7, which therefore do not meet the requirements of **Art. 33 (2) PCT**.

## Inventive Step (Art. 33 (3) PCT)

V.5. The prior art discloses several methods concerning antibody purification by caprylate precipitation.
Besides the documents cited above, **D3** (EP 0 893 450) discloses a process involving suspension of the antibodies at pH 3.8 to 4.5 followed by addition of caprylic acid and a **pH shift** to pH 5.0 to 5.2. After removal of precipitated proteins, caprylate is added to perform a second precipitation step. The supernatant is then passed over two different anion exchange resins.This method "maximizes yield and produces a gamma globulin with greater than 99% purity" (column 3, l.18-20).

V.6. The applicant found that a "pH shift ... is not needed to achieve a significant purification effect upon caprylate addition and removal of the resulting precipitate" (p.2, l. 18-20). The essential feature of the method disclosed in the present application is therefore considered to be "keeping the pH constant at pH 4.6 to 4.95 during the entire process of paste reconstitution and caprylate incubation and precipitate removal" (p.2, l. 20-23).

V.7. The closest prior art is considered to be D1, which discloses a caprylate precipitation at pH 4.8.
The subject-matter of claim 2 differs from D1 in that the anion exchange chromatography is performed at a different pH. The method of claims 3, 4, 6 and 8-22 differs from D1 in that a second anion exchange chromatography is performed and that certain conditions in the process are further specified.

V.8. The problem to be solved by the present application can therefore be seen as the modification of a purification process for IgG.
The solution to the problem is the performance of the chromatography at pH 5.0-5.2 instead of pH 5.7, and the further specification of pH adjustment, detergent treatment, UV-treatment, sterile fltration etc. during the production process.

V.9. Claims 1-23 do not involve an inventive step and do not meet the requirements of **Art. 33 (3) PCT** for the following reasons:
The modifications of said method only represent slight experimental changes, which are considered to lie within the scope of the common practice followed by a person skilled in the art. It is easy for a person trained in protein biochemistry to optimize the conditions for immunoglobulin purification via anion exchange chromatography, especially in light of D3. The additional features contained in the claims appear trivial and are considered workshop modifications. They are standard conditions in antibody purification and do not appear to lead to any surprising effects or advantages.

**Re Item VI**
**Certain documents cited**

**D5: WO 2005/073252 A (SUOMEN PUNAINEN RISTI VERIPALVELU; PARKKINEN, JAAKKO) 11 August 2005 (2005-08-11)**

**Re Item VIII**
**Certain observations on the international application**

VIII.1. Claims 1, 6 and 20 do not meet the requirements of **Art. 6 PCT** in that the matter for which protection in sought is not defined. The claims attempt to define the subject-matter in terms of the result to be achieved ("under conditions of/that...", "appropriate additive").

VIII.2. The terms "about", "essentially", "significantly binding/bound" in claims 1, 2 and 6

are vague and indefinite, so that they render the scope of the claims unclear.

## Claims

1. A method of preparing a purified, virus inactivated and virus safe antibody preparation from a starting solution comprising antibodies and contaminants, the method comprising the steps of:

   (a) adjusting the pH of the starting solution to about 4.6 to about 4.95, in particular to about 4.8 to about 4.95 to produce an intermediate solution;

   (b) adding caprylate and/or heptanoate ions to the intermediate solution and maintaining the pH ~~at about 4.6 to about 4.95, in particular~~ at ~~about~~ 4.8 to about 4.95, whereby a precipitate is formed and the antibodies are essentially present in the supernatant;

   (c) incubating the supernatant solution under conditions of caprylate and/or heptanoate ion concentration, time, pH and temperature optionally concentrating and diafiltrating the filtrated solution before pH adjustment;

   (d) applying the filtered solution with a least one anion exchange resin and optionally with two different anion exchange resins under conditions that allow binding of contaminants to the resin while not allowing significant binding of the antibodies to the resin, wherein a purified, virus inactivated and virus safe antibody preparation is produced.

2. The method of claim 1 wherein in step (d) the virus inactivated solution is contacted with the at least one anion exchange resin at a pH from about 5.0 to 5.2.

3. The method of claim 1 and/or 2 wherein a second anion exchange chromatography is performed at a pH range of from 6.7 to 6.9.

4. The method of claims 1 to 3 wherein steps (b) and (c) are repeated at least one time.

5. The method of claims 1 to 4 wherein the starting solution comprises plasma-derived antibodies.

6. The method of claims 1 to 5 wherein in step (d) the inactivated solution is contacted with two different anion exchange resins under conditions such

that contaminants are selectively bound to the resins while the antibodies, are not significantly bound to the resins.

7. The method of claims 1 to 6, wherein the antibodies are immunoglobulin G.

8. The method of claim 6, where the pH is adjusted to pH 6.8 ± 0.1 prior to the second anion-exchange chromatography.

9. The method of claims 1 to 8, wherein the anion-exchange chromatography flow-through is concentrated to 60 to 90 mg/ml and diafiltrated against a buffer solution, preferably a phosphate buffer.

10. The method of claims 1 to 9, wherein the flow-through of the first anion-exchange chromatography is solvent detergent treated, preferably by Triton X-100 and TnBP, most preferred by concentrations of 1% Triton X-100 and 0.3% TnBP for 4.5 to 8 hours to inactivate lipid coated viruses.

11. The method of claim 10, the detergents of the incubation mixture of which are removed by solid and liquid phase extraction.

12. The method of at least any one of claims 1 to 11 wherein at least one of the methods selected from the group consisting of UV-C treatment, heat-treatment, virus filtration and prion removal or inactivation is combined with a caprylate treatment of claim 1.

13. The method of claim 11, wherein the pH value upon solid phase extraction is adjusted to 6.7 to 6.9.

14. The method of claim 13, wherein the solution is submitted to the second anion-exchange chromatography.

15. The method of claim 14, wherein the pH value of the anion-exchanger flow-through is adjusted to 3.5 to 4.5, preferably to pH 4.0 ± 0.1.

16. The method of claim 15, wherein the IgG solution is contacted by a virus filter.

17. The method of claim 15, wherein the IgG solution is contacted by a nanofilter.

18. The method of claim 15 wherein the IgG solution is incubated for at least 24 hours, preferably at 37°C± 1.

19. The method of claim 15, wherein the IgG solution is concentrated to 5 or 10%.

20. The method of claim 19, wherein the osmolarity of the concentrate is adjusted to 200 to 400 mOsmol/kg by an appropriate additive.

21. The method of claim 20, wherein the IgG solution is pH adjusted to 3.5 to 6.0, preferred to a pH value of 4.0 to 5.5.

22. The method of claim 21 wherein the IgG solution is sterile filtered and filled in glass bottles or plastic containers.

23. An IgG containing fraction obtainable according one of the claims 1 to 22.